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THE PROGNOSTIC EFFECT OF NON-SPECIFIC MUSCULOSKELETAL PAIN IN OTHER BODY SITES ON THE TREATMENT OF NON-SPECIFIC NECK AND BACK PAIN

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Opinnäytetyön nimi

Muiden kehonalueiden epäspesifien tuki- ja liikuntaelimistön kipujen prognostinen vaikutus epäspesifin niska- ja selkäkivun hoidossa

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Tiivistelmä

Niska ja alaselkä ovat yleisimmät tuki-ja liikuntaelimistön kipualueet, ja niihin liittyy usein muiden kehon alueiden epäspesifejä tuki-ja liikuntaelimistön kipuja. Monikipuisuuden prognostinen arvo komorbiditeettina on kuitenkin epäselvä. Monikipuisuudella ei ole tarkkaa määritelmää, selkeää konsesusta, järjestelmällisiä tutkimusasetelmia eikä kohdennettuja hoitostrategioita. Tässä opinnäytetyössä monikipuisuus on määritelty kipuna kolmella tai useammalla kehonalueella viimeisen 6 kuukauden aikana, niska- ja/tai selkäkivun lisäksi.

Tämän opinnäytetyön tarkoituksena on arvioida epäspesifin monikipuisuuden mahdollista prognostista vaikutusta epäspesifin niska- ja/tai selkäkivun hoidossa.
Tämä opinnäytetyö on kvantitatiivinen seurannallinen kohorttitutkimus ja sekundäärinen analyysi satunnaistetusta kontrolloidusta tutkimuksesta, johon kerättiin aineisto ”BJÖRN-trial”-kyselyllä. Tutkimuspopulaatio (N=409) vastasi alkukyselyyn ja myöhemmin seurantakyselyihin 7 viikon ja 6 kuukauden kohdalla. Binomiaalisia regressioanalyysejä käytettiin tutkittaessa monikipuisuuden ja lopputuleman yhteyttä.

Kaikilla koehenkilöillä oli niska- ja selkäkipua, ja niskakipu oli yleisin vaiva (58 %). Tutkimuksen alussa monikipuisuutta raportoi 74 % koehenkilöistä (302/409). Niiden koehenkilöiden osuus tässä tutkimuksessa, jotka kokivat kliinisesti merkittävän paranemisen 6 kuukauden kohdalla niska- ja/tai selkäkivussa ja joilla oli lisäksi monikipuisuutta, oli 35 % (147/409). Analyysit monikipuisuuden prognostisesta vaikutuksesta paranemiseen niska-ja selkäkivun hoidossa osoittivat, että monikipuisuudella ei ollut vaikutusta prognoosiin 7 viikon eikä 6 kuukauden kohdalla.
Epäspesifillä tuki-ja liikuntaelimistön monikipuisuudella muilla kehon alueilla ei ole prognostista vaikutusta paranemiseen epäspesifin niska-ja selkäkivun hoidossa.

Asiasanat
monikipuisuus, niskakipu, selkäkipu, prognoosi, tuki- ja liikuntaelin kipu, komorbiditeetti

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The Prognostic Effect of Non-specific Musculoskeletal Pain in Other Body Sites on the Treatment of Non-specific Neck and Back Pain

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Abstract

Neck and low back are the most usual musculoskeletal pain sites and they are often accompanied by non-specific musculoskeletal pain in other body sites. However, the prognostic value of multi-site pain as comorbidity is unclear. Multi-site pain doesn't yet have a distinct definition, clear consensus, organized study design and targeted treatment strategies. In this thesis, multi-site pain is defined as pain in more than three anatomical body site during the last 6 months, in addition to neck and/or back pain.

The purpose of this thesis is to evaluate the possible prognostic effect of non-specific multi-site pain on the treatment of non-specific neck and/or back pain.
This thesis is a quantitative observational cohort study and a secondary analysis of a randomized controlled trial, for which the data was collected by using the "BJÖRN-trial" –questionnaire. The study population (N=409) answered a baseline questionnaire and later on a follow-up questionnaire at week 7 and 6 months in this study. Binomial regression analyses were used to investigate the associations between the multi-site pain and the outcome.

All participants had neck and/or back pain, and neck pain was the most common complaint (58%). At baseline multi-site pain was reported by 74% of the participants (302/409). The proportion that reported a clinically meaningful improvement in neck and/or back pain at the 6-month follow-up, and reported multi-site pain was 35% of the participants (147/409). The analyses of the relationship between the prognostic effect of multi-site pain on the recovery on the treatment of neck and/or back pain showed that multi-site pain did not have an effect on the prognosis at the follow-ups of 7 weeks or 6 months.
Non-specific multi-site musculoskeletal pain in other body sites did not have a prognostic effect on the recovery on the treatment of non-specific neck and/or back pain.

Keywords
multi-site pain, neck pain, back pain, prognosis, musculoskeletal pain, comorbidity

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1 BACKGROUND

Naprapathy has been studied intensively during the last decade. Manual therapy such as naprapathy has been discovered to be without a doubt an effective treatment for musculoskeletal disorders. Schools providing education on naprapathy are located in Kotka, Finland; Stockholm, Sweden; New Mexico, USA and Chicago, USA. Research in naprapathy is mainly executed in Karolinska Institutet, Stockholm. One of the leading researchers in the field of naprapathy is Eva Skillgate (D.N, PhD) who works as an associate professor at Karolinska Institutet. The first contact to Eva Skillgate was made by the authors of the thesis in spring 2014 concerning co-working. Skillgate agreed to be the supervisor and a decision was made to execute a secondary analysis on the data from the study “Naprapathic Manual Therapy or Evidence-Based Care for Back and Neck Pain: A Randomized, Controlled Trial”.

2 INTRODUCTION

Multi-site pain is defined as pain in more than one anatomical body site simultaneously or during a specific period of time with no other ailment that could explain the pain. So far multi-site pain does not have a distinct definition and a clear distinguishable consensus. There is no clear or organized research into this population and no targeted treatment strategies.

Widespread pain and fibromyalgia

Widespread pain has been classified by the American college of rheumatology (ACR) in 1990 as: pain that is present for three months on the left and right side of the body and pain above and below the waist. Furthermore, axial skeletal pain (cervical spine, anterior chest, thoracic spine or low back) has to be present. (Wolfe et al., 1990, 163-169.) For example, pain in the low back, left knee and right shoulder would be classified as widespread pain according to the ACR.

A Manchester definition of chronic widespread pain differs from the ACR definition: pain has to be reported in at least two parts of two contralateral limbs and as well in the axial skeleton for at least three months. Therefore, a stricter

definition has been made and it has a stronger association with factors that describe best a patient with chronic widespread pain. These factors are older age, reporting at least one “non-pain” somatic symptom and high levels of fatigue. These patients also have significantly more psychological distress, low levels of self-care and hypochondrical beliefs. (Hunt et al., 1999, 276-277.)

The ACR and Manchester definitions of chronic widespread pain both give one sort of explanation and viewpoint for multi-site pain patterns. Multi-site pain can be demonstrated as different patterns as well. Many pain patterns can appear in the upper and lower body independently. It has been suggested that a site specific chronic musculoskeletal pain could be an early stage of or a determinant of chronic widespread pain. (Carnes et al., 2011, 82.)

The most sensitive, specific and accurate way to discriminate between widespread pain and fibromyalgia is the presence of 11 of 18 tender points with simultaneous widespread pain when labeled as fibromyalgia (Wolfe et al., 2010, 163-169). The ACR created a new diagnostic tool for fibromyalgia in 2010 where a physical or a tender point examination was no longer required. New diagnostic tool includes a widespread pain index (WPI) and a symptom severity scale for fibromyalgia (SS). (Wolfe et al. 2010, 604-608.)

Widespread pain versus multi-site pain

The results from a UK population study by Carnes et al. show clearly that chronic multi-site pain differs from chronic widespread pain. They defined chronic widespread pain according to the ACR classification and multi-site pain was defined as pain in two or more body sites. Total 67% of the patients that had chronic multi-site pain did not meet the criteria for the definition of chronic widespread pain. (Carnes et al., 2007, 1168-1169.) In another study, 19% of the patients with pain in 6-10 sites did not meet the criteria for widespread pain and 67% of the patients with 4-5 pain sites did not either meet the criteria for widespread pain. (Coggon et al., 2013, 1773)

Chronic multi-site and widespread pain have common factors that are significant for the exposure. These factors include female gender, older age, psychological distress, high pain intensity and high disability (Carnes et al., 2007,

1169). The range of pain in widespread and multi-site pain, that is, the higher number of pain sites, is mainly associated with the increase of distress, pain intensity and disability.

Carnes studied patterns of chronic pain in a survey of 2493 people in England and noted that multi-site pain does not follow the same acknowledged and distinguishable patterns that can be seen in referred pain, neural dysfunction or irritation of the nerve roots. Consequently, chronic multi-site pain is normally researched and classified in the same way as chronic widespread pain or fibromyalgia since they have established definitions. (Carnes 2011, 82.)

Pain sites and prevalence

Low back pain is the most common musculoskeletal complaint followed by neck pain and shoulder pain (Coggon et al., 2013, 1772). Most of the studies concentrating on musculoskeletal pain are focused on one pain site such as low back, but it is very usual that pain in any anatomical site is accompanied by pain in any other site (Ligthart et al., 2014, 949). Even though low back pain is common, it must be noted that when a population of 2445 people were studied in England, the prevalence of single-site chronic low back pain was 3%, and even when upper leg pain was included as referred pain, the number was only 4% (Carnes et al., 2007, 1169). Pain in bilateral sites of the body is very usual, meaning if there is pain in the right knee there is a high probability to have pain in the left knee also. Adjacent anatomical pain in the upper limb is usual (for example neck pain together with shoulder pain or shoulder pain with ipsilateral elbow pain), but it is not as common as bilateral pain. (Coggon et al., 2013, 1773.)

Multi-site pain has been studied recently worldwide in 47 occupational groups in 18 countries (Coggon et al., 2013, 1773). The prevalence for pain at least in two or more different body sites varies between 20 to 40% (Haukka et al., 2013, 308; Rathleff et al., 2013, 4; Solidaki et al., 2010, 57; Yeung et al., 2002, 2168) and it is very often noted that multi-site pain is much more common than single site pain (Carnes et al., 2007, 1770; Kamaleri et al., 2008a, 43; Natvig et al., 2001, 22; Parot-Schinkel et al., 2012, 3; Solidaki et al., 2010, 60; Yeung et al., 2002, 2171). Taking into account the frequency of multi-site pain,

it may be beneficial to start observing musculoskeletal pains as an entirety where one pain site affects the other, and vice versa.

Sometimes there is one pain location that can be labeled as the primary complaint and other pain sites can be labeled as comorbidities. In a study by Hartvigsen et al. (2013,45) of 4817 Danes, it was noted that if a primary complaint was in the spine (neck, upper, back, low back) there was a high probability for pain in the other areas of the spine. Previous studies have found out that 37-80% of the patients with low back pain report other musculoskeletal pain complaints (Gore et al., 2012, E671; Ijzelenberg and Burdorf, 2004, 809-810; Molano et al., 2001, 277; Parot-Schinkel et al., 2012, 3; Yeung et al., 2002, 2168) and 80% of the patients with sub-chronic or chronic pain in the neck, upper back, hip, or elbow report also other musculoskeletal pain sites (Parot-Schinkel et al., 2012, 3).
Back pain is most usually accompanied by pain in the neck, knee, upper extremities, shoulder or upper back (Ijzelenberg and Burdorf, 2004, 809; Molano et al., 2001, 277; Webb et al., 2003, 1997; Yeung et al., 2002, 2169), whereas the most common pain sites associated with neck pain are shoulder, back and knee (Côté et al., 2000, 1112; Webb et al., 2003, 1997).

It should be noted that there is usually no data whether the several pain sites occurred simultaneously or as separate episodes during the observed period (Kamaleri et al., 2008a, 45). Many studies observe the occurrence of multi-site pain during an episode of 1-12months (Coggon et al., 2013, 1771; Ijzelenberg and Burdorf, 2004, 807; Solidaki et al., 2010, 56). One pain site may cause the appearance of the other or the sites can occur as independent episodes of their own without having a significant effect on each other.

Risk factors, associations and prognostic effect of multi-site pain

Pain in two to four musculoskeletal sites is already present and common in adolescents 16-18 years of age, and it must be noted that multi-site pain is persistent by its nature. Many lifestyle and psychological factors such as emotional and behavioral problems, long period spent sitting, short sleep time, smoking, overweight and high physical activity level have a vast effect on the

development of pain sites and they predict the persistency for multi-site pain among adolescents. (Paananen, 2011, 57, 59-60, 71.)

Patients with multi-site pain are more often female, have poorer self-reported general health, more sleeping problems, more psychological problems, high pain intensity, and high or low BMI (Natvig et al., 2001, 22; Kamaleri et al., 2008b, 744-746). Low and moderate leisure time physical activity at baseline is connected with a persistently high prevalence of multi-site pain, and obesity predicts an increased prevalence of multi-site pain and vice versa (Haukka et al., 2012, 487-488). Also, factors such as sleep quality and education need to be taken into consideration (Kamaleri et al., 2009a, 27). Along with the increasing number of pain sites there is a decrease in functional ability, sleep quality, psychological health and educational level (Kamaleri et al., 2008b, 745-746; Kamaleri et al., 2008a, 43; Ijzelenberg and Burdorf, 2004, 809). Patients with low back pain and other musculoskeletal pains have impaired general health and lowered health related quality of life. They also have high pain intensity and are more disabled than those with low back pain as their only ailment. (Ijzelenberg and Burdorf, 2004, 809.)

Risk factors for multi-site pain have been studied mostly with regards to work-related factors and in a working population. Being a female, older age, reporting two or more distressing somatic symptoms, exposure to multiple physically loading activities, adverse psychosocial and psychological factors, somatization, exposure to considerable vibrations, exposure to jolts and current or previous smoking (only in females) are the strongest predictors for multi-site pain (Coggon et al., 2013, 1773-1774; Haukka et al., 2011, 434-436; Haukka et al., 2012, 487-488; Solidaki et al., 2010, 57-58; Herin et al., 2014, 940-941).

As noted before, multi-site pain has a very persistent nature. Kamaleri et al. studied the number of pain sites with a follow-up of 14 years and there was only a 0.5 increase in the mean number of pain sites between the baseline (average of 3.7 pain sites) and the follow-up (average of 4.2 pain sites). Even after 14 years 46.2% of the patients reported the same number or one pain site more or less. (Kamaleri et al., 2009a, 27.) Having low job control and high physical workload increase the risk of having persistent multi-site pain (Haukka, et al. 2011, 434-436; Haukka et al. 2012, 487-488). The number of

pain sites reported at baseline is by far the most important predictor of multi-site pain at follow-up (Haukka et al., 2012, 487-488) it is also a strong predictor of future work disability and work absenteeism (Haukka et al., 2013, 311; Kamaleri et al., 2009b, 428-429; Miranda et al., 2010, 451; Neupane et al., 2011, 565-568). The prognostic effect of multi-site pain on the treatment of neck and low back pain –which are among the most common pain sites- (Coggon et al., 2013, 1772; Parot-Schinkel et al., 2012, 3; Picavet and Schouten, 2003, 169, Hartvigsen et al., 2013, 454), should be studied because it is one of the factors that can be modified (Dunn et al., 2011, 316).

Prognosis of neck and back pain

The prognosis of neck and back pain has been studied extensively, yet there are many uncertainties. Many prognostic factors for neck and back pain have been extensively examined through research and evaluated in literature. Some can therefore be regarded as important factors that have a prognostic effect on the recovery of neck and back pain.

The outcome in the studies of neck and low back pain can be short-term and/or long-term. Prognostic factors may vary between short-and long-term outcomes (Hovinga et al., 2004, 641-643), but what is relevant is that both neck and low back pain have a re-occurring and persistent nature (Carroll et al., 2008a, s80; Carroll et al., 2008, s113; Hestbaek, 2003, 161; Van Oostrom, 2011, 996). That in mind, short-term outcomes may not be that relevant since the outcomes might present only a small recovery period in a re-occurring neck or low back pain. In other words, it is not a full recovery. (Hestbaek, 2003, 150, 162-163.)

The following literature review focuses on prognostic factors in neck and low back pain among the working and general population, which may differ. Neck and back pain are common health complaints, and it is important to know the factors that have an influence on the prognosis. It is beneficial to know the prognostic factors, thus helping healthcare practitioners in planning the care for the patients.

Neck pain

There is consistent evidence showing that younger age has a prognostic value among the general population for a better recovery as the outcome, and older age comes with a poorer prognosis, contributing to functional disability in performing different activities in a deteriorating manner and making the pain more persistent (Carroll et al., 2008a, s78, s91). In contrary to the general population, among the working population the evidence shows that age is not a prognostic factor in the neck pain (Carroll et al., 2008b, s96). Among the general population female gender has some prognostic effect for a poor outcome in the neck pain (Carroll et al., 2008a, s78). Similarly, among the working population female gender might have some prognostic effect for a poor outcome in the neck pain, but the results are not as strong as among the general population. (Carroll et al., 2008b, s96.)

Health and pain-related factors that affect the prognosis on the recovery among the general population are initial pain intensity, duration of neck pain, history of neck or shoulder pain/symptoms, history of neck injury, low back pain as a comorbidity, poor self-perceived general health, multiple musculoskeletal symptoms and bad or moderate quality of life (Hovinga et al., 2004, 643-644; Carroll et al., 2008a, S79). Among the working population, the effect of health and pain-related factors somewhat differ from the general population. History of neck pain comes with a poorer prognosis also among the working population, but other similarities are not found. Among the working population a prior sick leave and prior musculoskeletal pain predict a poorer outcome. (Carroll et al., 2008b, s96). Among the general population, in contrary to the working population, prior sick leave has not been found to have a prognostic effect (Carroll et al., 2008a, s79).

Regarding socioeconomic factors, among the general population the unemployed have a higher likelihood of reporting the same pain one year later than the employed (Carroll et al. 2008a, s79), and a low level of education tends to be associated with a poor outcome (Hovinga et al., 2004, 643-644). Job type/classification is the only socioeconomic factor that has been found to have a prognostic value among the working population, according to the

knowledge of the authors of this thesis. In contrast to general believes physical, ergonomic and job demand factors do not have an effect. (Carroll et al., 2008b, s97.)

Psychological factors such as passive coping (worrying, fear avoidance) and passive coping strategies (becoming angry or frustrated) are the strongest prognostic factors for a poor outcome in neck pain among the general population (Carroll et al., 2008a, s79). Among general population, there is a higher probability of recovery with moderate and high expectations of recovery before the treatment (Palmlöf et al., 2016, 5). Unlike among the general population, psychological and social factors have not been found to affect the course of neck pain among the working population (Carroll et al., 2008b, s97).

It has been found out that exercising has a prognostic value among the working population, but not in the general population (Carroll et al., 2008b, s97; Carroll et al., 2008a, s79). Among the working population, exercise, that is, physical activity and participation in sporting activities, lead to a better outcome in neck pain and improvement in chronic neck pain (Carroll et al., 2008b, s97) and higher physical activity, especially among women, has a connection with recovery from neck pain (Rasmussen-Barr et al., 2013, 2080).

Low back pain

The prognosis and natural course of acute and persistent low back pain usually follows a pattern where pain and disability decrease in the first six weeks. After six weeks up to 12 months the improvement begins to slow down, and only small rates of reduction in mean pain and disability can be seen. Within one year, acute low back pain patients can expect to have minimal pain and disability. Chronic low back pain patients may expect to have moderate levels of pain and disability. (Menezes Costa et al., 2012, E620-E621.)

There is clear evidence that age is a prognostic factor among the working population and general population. Older age comes with a poor outcome in both populations. (Thomas et al., 1999, 1663–1664; Hayden et al. 2009, p. 787–788; Van Oostrom et al., 2011, 996.) According to the majority of the studies, women tend to have a poor outcome more often than men among

both general and working population (Hayden et al. 2009, p. 787-788; Campbell, 2013, 876; Enthoven et al., 2006, 140; Thomas et al., 1999, 1663-1664).

Health and pain-related factors are partly same among the general and working population, but there are some differences. High functional disability, longer episode duration and poor general health are predictors for poor outcome among the general population (Dunn et al., 2011, 315; Thomas et al., 1999, 1663-1664) and among the working population (Enthoven et al., 2006, 140; Hayden et al. 2009, p. 787-788). Factors that predict a poorer outcome only among the general population are high pain intensity, history of low back pain and upper body pain, especially combined with leg pain (Dunn et al., 2011, 316; Thomas et al., 1999, 1663-1664). The factor indicating a poorer prognosis only among the working population is sciatica (Hayden et al. 2009, p. 787-788). The effect of pain can also be seen among the working population but in a different way; instead of high pain intensity, higher pain frequency has a prognostic effect for poor outcome (Enthoven et al., 2006, 140).

Socioeconomic factors have an important role in the prognosis among both populations. Unemployment, absence from work, belief that pain is related to work, dissatisfaction with current employment or work status indicate a poorer prognosis among the general population (Thomas et al., 1999, 1663-1664; Dunn et al., 2011, 315-316; Van Oostrom et al., 2011,996). Lower social class and low education level have been shown to have a prognostic effect for a poorer outcome only among the general population (Campbell, 2013, 876). Among the working population, the factors that indicate a poor outcome are poor relations with colleagues, physically heavy work, and presence of worker's compensation (Hayden et al. 2009, p. 787-788).

The psychological factors that have been found out to affect the prognosis among both working and general population are increased/high levels of physiological or psychosocial stress (Thomas et al., 1999, 1663-1664; Hayden et al. 2009, p. 787-788). Anxiety, catastrophizing and belief that his or her low back pain will last for a long time indicate a poorer prognosis only among the general population (Dunn et al., 2011, 315; Campbell, 2013, 879; Grotle, 2010, 8).

Low level of exercise has a prognostic effect for a poorer outcome among both the general and the working population (Enthoven et al., 2006, 140; Thomas et al., 1999, 1663-1664). Among the general population, current or previous smoking and a low alcohol intake have some prognostic value, predicting a poorer outcome (Thomas et al., 1999, 1663; Van Oostrom et al, 2011, 996).

Spinal pain

Since neck and back pain are clearly associated with each other, it is beneficial to examine them together, (Kääriä et al. 2009, 409 -410). A study that examined spinal pain, defined as neck and/or back pain, among the working population, indicated that sleep is an important prognostic factor. Patients who sleep sufficiently have a significantly higher chance for a recovery from non-specific spinal pain compared to patients with impaired sleep. The patients who sleep sufficiently have approximately a two-fold improvement in pain and pain-related disability compared to patients with impaired sleep at a 12-month follow-up. (Paanalahti et al. 2016, 762-763.)

Another study concerning spinal pain among the general population reached a conclusion that women have more often spinal pain than men and they have twice as often psychological distress (anxiety, depressed mood, social function and loss of confidence) as comorbidity. Spinal pain and psychological distress together worse the prognosis of recovery when compared to recovery with either spinal pain or psychological distress. The poorest prognosis comes with having all three conditions together (neck pain, back pain and psychological distress). It is common that people with spinal pain as a single condition develop psychological distress later and vice versa. (Paanalahti et al., 2014, 1932–1933.)

Research questions

The purpose of this thesis is to examine the prognostic effect of other non-specific musculoskeletal pain complaints in population receiving treatment for non-specific neck and/or back pain.

The research questions are:

1. What is the proportion of participants with neck and/or back pain included in a randomized controlled trial that have non-specific multi-site musculoskeletal pain in other body sites at baseline?
2. What is the proportion of participants in the trial that have recovered from neck and/or back pain at the 6 months follow-up that have non-specific multi-site musculoskeletal pain in other body sites?
3. What is the prognostic effect of non-specific multi-site musculoskeletal pain in other body sites on recovery from neck and/or back pain?

3 PAIN

3.1 Defining pain

Acute pain is an unpleasant sensation caused by noxious stimuli. The purpose of it is to avoid possible and further tissue damage. The sensation of pain is transmitted to the central nervous system by nociceptive pathways that are activated by thermal, chemical or mechanical stimuli. (Kalso et al., 2009, 77.) Acute pain causes a reflex to withdraw from the noxious stimuli to avoid further tissue damage. Usually the cause of acute pain is well known and treatable. (Kalso et al., 2009, 105-106.)

Pain is defined as chronic when it has lasted for more than three months or when pain has lasted longer than it takes for the tissue to recover. Chronic pain can be caused by damage and/or changings in the nervous system or by

some basic disease (such as rheumatoid arthritis). Chronic pain is more complex and multidimensional than acute pain and it has psychosocial effects such as fear-avoidance and catastrophizing. (Kalso et al., 2009, 106-109.)

Pain can also be divided into nociceptive or neuropathic pain. It is categorized as nociceptive when it is initiated by tissue damage and it is usually accompanied with inflammation. When the healing process is completed, the pain sensation vanishes and inflammatory pain hypersensitivity returns back to normal. Pain is categorized as neuropathic when there is a lesion or pathological function in the nervous system. (Woolf and Salter, 2000, 1765.)

Pain is categorized as idiopathic when no nociceptive and no neuropathic origin can explain the underlying cause for the pain and often the origin is a mystery. When psychiatric conditions such as depression and anxiety precede the pain, then pain is categorized as psychogenic pain. (Kalso et al., 2009, 157.)

3.2 Central sensitization

The phenomenon of central sensitization is strongly related to conditions such as widespread pain and fibromyalgia. In central sensitization, there is abnormal responsiveness and increased gain of the nociceptive system due to changes in the central nervous system. Amplified and prolonged responses to noxious and non-noxious inputs are the result from facilitated excitatory synaptic responses and simultaneously depressed inhibition. (Woolf and Salter, 2000, 1766; Graven-Nielsen and Arendt-Nielsen, 2002, 313.) In central sensitization, painful sensations may occur even in the absence of either peripheral pathology or noxious stimuli (Latremoliere and Woolf, 2009, 896). Hyperalgesia, allodynia and referred pain are all manifestations associated with central sensitization (Meeus and Nijs, 2007, 470).

4 MATERIALS AND METHODS

4.1 Study design

The current thesis is a quantitative observational cohort study. This thesis is a secondary analysis that utilizes material already collected by others; in other words, secondary material (Hirsijärvi et al., 2008, 181-182). The material examined in this study was originally collected for a study called “Naprapathic Manual Therapy or Evidence-Based Care for Back and Neck Pain: A Randomized, Controlled Trial” by Skillgate et al. and it was published in Clinical Journal of Pain at 2007 and in BMC at 2010. The study has the name “BJÖRN-trial” and it has been executed in Stockholm, Sweden. The purpose of the original study was to compare naprapathic manual therapy to evidence-based care provided by a physician for participants with non-specific neck and/or back pain. A large amount of data was collected at the baseline by using the “BJÖRN-trial” –questionnaire. In this current thesis, the exposure is measured with questions from the section C1 (See appendix 1 and 2). The necessary material for the thesis was provided by Eva Skillgate at the Institute of Environmental Medicine, Karolinska Institutet in 2015.

4.2 Ethics approval and consent to participate

The trial was approved by the Ethical review board in Stockholm, Sweden (03-657 and 2014/190-32). Informed consent was received from all study participants including consent for publication of the results. All data analyses were performed at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm.

4.3 Recruitment to the BJÖRN-trial

The participants were recruited by advertising in two major public companies in Stockholm, Sweden, from March to September in 2005. The number of potential participants was 40,000, and they were mainly women and working in the healthcare sector, schools and in the postal service. The participants who met the inclusion criterion were asked to contact the study administration. Inclusion criterion was the presence of neck and/or back pain (lasting at least two weeks and causing marked dysfunction at work or in leisure time).

In the first stage of the exclusion, the criteria were: 1) too mild symptoms, 2) pregnancy, 3) a specific diagnose such as acute slipped disc or spinal stenosis, 4) inability to understand Swedish, 5) visits to a naprapath in the preceding 2 months or another manual therapist in the preceding month with the exception of massage. Participants meeting the criteria in the trial were asked to visit the study center for a clinical screening. At the study center, the participants gave their approval for the trial, answered an extensive self-administered questionnaire and were examined by an experienced physician (1 of 4). Physicians used a standardized form, made a diagnosis, and prescribed medication if necessary.

In the second stage of exclusion, performed by the physician, the exclusion criteria were: 1) too mild symptoms (the physician's subjective opinion based on the estimated pain and disability in the questionnaires filled in before the examination, and the results of the anamnesis and physical examination), 2) evidence-based advice during the past month, 3) surgery in the painful area, 4) acute prolapsed disc, 5) spondylolisthesis, 6) stenosis, 7) "red flags"(older than 55 when the pain appearing for the first time, recent trauma in the region, constant pain or pain worsening in the night, cancer in the past or at present, consumption of steroids now or recently, drug abuse, HIV, very bad general health, significant weight loss, very bad disability, intensified pain at the smallest movement, obvious structural deformity of the spine, saddle anesthesia/sphincter disturbance, extended muscle weakness, inflammatory or rheumatic diseases, marked morning stiffness, long-lasting severe disability, or peripheral joints affected).

The included participants (N=409) were randomized to one of two interventions with the aim of comparing naprapathic manual therapy (index group) and evidence-based care provided by a physician (control group). The Naprapathic manual therapy treatments (6 treatments within 6 weeks) were given by one of eight experienced licensed naprapaths and included spinal manipulation/mobilization, massage and stretching. Evidence-based care was provided by one of four experienced physicians (two times or more if needed) and it was defined as support, advice on staying active and pain coping strategies

according to the best scientific evidence available. In this study, the study population was combined and then divided to three subgroups according to the number of pain sites.

4.4 Exposure and outcome

The exposure in the present thesis, non-specific pain in other musculoskeletal sites, was assessed in the baseline questionnaire with the question" Have you had any symptoms (pain, ache, discomfort) sometime in the last 6 months in the". The possible pain sites were shoulder/shoulder joint, elbows, wrists/hands, hips, knees and ankles/feet, Yes/No. The highest number of possible pain sites was 12 in addition to neck and/or back pain. (See appendix 1 and 2)

For the analyses, the study population was divided in three groups according to the number of other non-specific musculoskeletal pain sites. The first group (MSK0, n=107) had neck and/or back pain but no other non-specific musculoskeletal pain sites or one to two other non-specific musculoskeletal pain sites. The second group (MSK1, n=184) had neck and/or back pain and three to five other non-specific musculoskeletal pain sites. The third group (MSK2, n=118) had neck and/or back pain and six or more non-specific musculoskeletal pain sites.

The study population was followed prospectively with web-based questionnaires or a questionnaire sent by mail to measure the outcomes. The outcome in this analysis is a clinically meaningful improvement in pain measured with a slightly modified Chronic Pain Questionnaire (CPQ) that Von Korff originally developed (Von Korff et al., 1992). Originally the questions in the questionnaire concerned the past 6 months but it was changed to concern the last 4 weeks instead. Current pain, worst pain and average pain were rated by the participants with numeric rating scales 0-10 (0= no pain, 10= worst pain) at baseline and follow-up at weeks 7 and 24. The pain score was the mean of these three items. A clinically meaningful improvement in pain was defined as a decrease of at least two steps when the follow-up score was compared to the baseline score. The amount of pain sites was not measured at the follow-ups of weeks 7 and 24.

4.5 Potential confounding factors

Information from the “BJÖRN-trial” baseline questionnaire was used to identify potential confounding factors in the association between the exposure and the outcome when doing the analysis. The potential confounding factors included age (continuous), sex (male/ female), pain related factors, history of previous episode, education, depression, sleeping problems, smoking, physical inactivity, job dissatisfaction, pain related disability at baseline and treatment (Table 1).

Pain related factors included pain intensity at baseline (continuous variable) and duration of current pain episode (2-4weeks/ 1-3moths/ 3-6 months/ 6-12 months/ >12 months) and history of previous episode of similar symptoms (yes/no). Education was categorized as elementary school (1-9 years), high school/vocational school (10-12 years,) university/college (13-16 years) and higher academic education (16 years or more). Depression had the alternatives of current/ had it in the past/ never had it. In the analyses the alternatives for daily smoking were yes/no. Physical activity was measured in three levels: exercise with high exertion level, medium exertion level and low exertion level for at least 20 minutes per exercise occasion. Physical inactivity was defined as answering never/irregularly to all three levels. Sleep quality were assessed with questions “Do you have trouble falling asleep” and “Do you wake up several times at night and sometimes have difficulty going back to sleep”. The study participants who answered that they had several times per week or always, every day to both questions were considered having sleeping problems. Job dissatisfaction was defined as choosing “I do not particularly enjoy it” or “I do not enjoy it at all”. Treatment was either naprapathic manual therapy or advice to stay active.

Table 1. Tested confounders

Confounder
Age
Sex
Pain at baseline
Duration of current episode
History of previous episode
Education
Depression
Sleeping problems
Smoking
Physical inactivity
Job dissatisfaction
Disability score
Treatment

4.6 Statistical analysis

Binomial regression analyses were used to investigate the associations between the exposures and the outcome. The results are a clinically meaningful improvement in pain measured at 7 weeks and 6 months as relative risks (RR) with a confidence interval of 95% (95% CI). The potential confounders were tested one by one in the crude model. A ≥10% change in the crude RR was considered to be a confounder and therefore added as a covariate in the final model. Stata version 12.0 was used as the statistics program for the analyses.

5 RESULTS

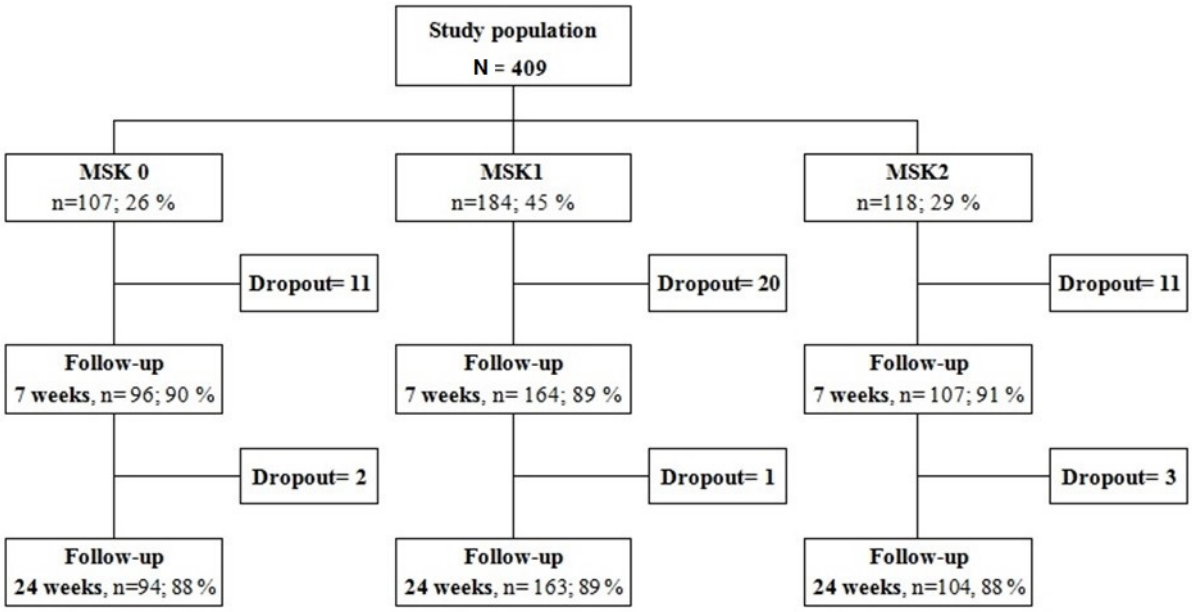

Figure 1. Flow chart describing the progress of the participants through the trial.

The study population (N=409) had a mean age of 47(SD 10) and 71% of the participants were women. All participants had neck and/or back pain, and neck pain was the most common complaint (58%). The mean pain at baseline was 4, and in 55% of the cases pain had lasted over 12 months. The majority of the population had had previous episodes of the current pain and had never had depression. The education levels of the study population were: elementary school (1-9 years) 12%, high school/vocational school (10-12 years) 34%, university/college education (13-16 years) 46%, higher academic education (>16 years) 8%. Nearly half (44%) of the participants had sleeping problems. Daily smoking was unusual (14%) and only small portion were physically inactive (13%). 107 of the participants reported neck and/or back pain and no other non-specific musculoskeletal pain sites or one to two other non- specific musculoskeletal pain sites. 184 of the participants reported neck and/or back pain with three to five other non-specific musculoskeletal pain sites and 118 reported neck and/or back pain with six or more non-specific musculoskeletal pain sites. Participants who had more pain sites were more often women, dissatisfied with their job, had pain lasting more than 12months, had previous episodes of pain, had depression in the past, had sleeping problems, smoked daily and took prescription medication more often in general. (See Figure 1 and Table 2)

Table 2. Characteristics

Characteristics	ALL (N=409)	MSK0 (n=107)	MSK1 (n=184)	MSK2 (n=118)
Mean age, years (SD)	47 (10)	44 (11)	47 (10)	49 (9)
Women%	71	58	70	86
Location of worst pain %				
Neck %	58	60	60	53
Low back %	36	40	34	34
Neck and low back %	6	0	6	13
Mean pain at baseline, 0-10 (SD)[a]	4 (2)	4 (2)	4 (2)	4,5 (2)
Duration of pain, %				
< 3 months	26	32	23	24
3-12 months	19	24	16	18
>12months	55	44	61	59
Previous episodes, %	86	81	87	90
Education at least, %				
1-9years	13	10	10	19
10-12years	34	33	32	36
13-16years	46	50	50	37
>16years	8	8	9	8
Depression, %				
have it	3	2	4	3
had it in the past	7	15	19	25
never had it	77	83	77	72
Sleeping problems, %[b]	44	13	10	21
Daily smoking, %	14	10	11	21
Physically inactive, %[c]	13	12	11	16
Job dissatisfaction, %[d]	9	6	8	13
Mean disability score, 0-10 (SD)[e]	3 (2)	3 (2)	3 (2)	3 (2)
Treatment, %				
Naprapathic manual therapy	50	45	53	52
Advice to stay active	50	55	47	48
Prescription medication				
Daily	14	2	2	10
Sometimes	21	16	22	25
Never	74	82	76	65

[a] CPQ, mean of the scales, NRS 0-10
[b] Answers from 5 to 10 (NRS 0-10), at question “How much do your neck/shoulder/thorax/low back pain symptoms interfere with sleep”,
[c] Combination of answers “Never”, “Irregularly”,” 1 time per week” at questions: “High exertion level (you have pulse, you feel strained and become sweaty” and “ Medium exertion level(effort that would make it difficult to hold a conversation with someone)
[d] Combination of answers “I do not enjoy it at all” and “I do not particularly enjoy it” at question: “In general, do you enjoy your work/work tasks?”
[e] WDQ+CPQ (disability part), mean of the scales, NRS 0-10 (WDQ= a modified version of the Whiplash Disability Questionnaire where the word “whiplash” was replaced with “back or neck pain”)

When the potential confounding factors were tested, it was found out that the only factor that confounded the association between the exposure and the outcome was the duration of current episode and it was therefore added in the final model of the analysis.

Tables 3 and 4 show the “risk” (RR) for a clinically meaningful improvement from baseline to follow-ups for the different exposures of multi-site pain, MSK0 being the reference group.

The proportion of participants with neck and/or back pain and were included in a randomized controlled trial that reported multi-site pain at baseline was 302 of 409 participants (74%) (MSK1 n=184, MSK2 n=118). The proportion of participants in the trial that had multi-site pain and a clinically meaningful improvement in neck and/or back pain at the 6-month follow-up was 147 of 409 participants (35%) (MSK1 n=89, MSK 2 n=58). The analyses of the relationship between the prognostic effect of multi-site pain with the recovery of neck and/or back pain showed that multi-site pain did not have an effect on the prognosis neither at the follow-up of 7 weeks (MSK1: 1,23 (0,97-1,56), MSK2: 0.98 (0,74-1,30) or at 6 months (MSK1: 1,10 (0,85-1,31), MSK2: 1,10 (0,85-1,35).

Table 3. Recovery at 7 weeks follow-up presented as Relative Risks (RR) and 95% Confidence Intervals (CI)

	Number of recovered/total	Crude RR (95% CI)	Adjusted RR (95% CI)*
MSK0[a]	47/107	1,0(ref)	1,0(ref)
MSK1[b]	95/184	1,18(0,93-1,51)	1,23(0,97-1,56)
MSK2[c]	51/118	0,97(0,73-1,29)	0,98(0,74-1,30)

*****Adjusted for duration of current episode

[a]MSK0: neck and/or back pain with no other non-specific musculoskeletal pain sites or one to two other musculoskeletal pain sites.

[b]MSK1: neck and/or back pain and three to five other non-specific musculoskeletal pain sites.

[c]MSK2: neck and/or back pain and six or more non-specific musculoskeletal pain sites.

Table 4. Recovery at 24 weeks follow-up presented as Relative Risks (RR) and 95% Confidence Intervals (CI)

	Number of recovered/total	Crude RR (95% CI)	Adjusted RR (95% CI)*
MSK0[a]	55/107	1,0(ref)	1,0(ref)
MSK1[b]	89/184	0,93(0,75-1,20)	1,10(0,85-1,31)
MSK2[c]	58/118	0,95(0,75-1,21)	1,10(0,85-1,35)

*****Adjusted for duration of current episode

[a]MSK0: neck and/or back pain with no other non-specific musculoskeletal pain sites or one to two other musculoskeletal pain sites.

[b]MSK1: neck and/or back pain and three to five other non-specific musculoskeletal pain sites.

[c]MSK2: neck and/or back pain and six or more non-specific musculoskeletal pain sites.

6 DISCUSSION

6.1 Main findings and relation to other studies

In this quantitative observational cohort study, it was found out that the number of participants with non-specific neck and/or back pain that were included in a randomized controlled trial and reported non-specific musculoskeletal multi-site pain at baseline was 74% (302/409). The prevalence of multi-site pain as a comorbidity to neck and/or back pain is similar to the findings of other studies with the percentage varying from 37 to 80% (Gore et al., 2012, E671; Ijzelenberg and Burdorf, 2004, 809-810; Molano et al., 2001, 277; Parot-Schinkel et al., 2012, 3; Yeung et al., 2002, 2168).

Similarly to earlier studies, in this thesis participants with more pain sites were more often female and had sleeping problems. Psychological problems are also somehow connected to multi-site pain. In this thesis depression in the past was associated with having more pain sites, and it has been noted before that patients with more pain sites have more psychological problems. Patients with more multi-site pain have been found to have high pain intensity, but no such connection was found in this thesis. (Natvig et al., 2001, 22; Kamaleri et al., 2008b, 744-746). Dissatisfaction with work was associated with more pains sites, and earlier studies have found out that having a low job control and high physical workload increase the risk of having persistent multi-site pain (Haukka, et al. 2011, 434-436; Haukka et al. 2012, 487-488). Participants with more pain sites also smoked daily more often. Smoking has been found out to predict the development and persistence of multi-site pain among adolescents (Paananen, 2011, 57, 59-60, 71.) and Herin et al. noted that current or previous smoking is a risk factor for multi-site pain among adult females. As Herin et al. also concluded it has to be noted that findings about the association of smoking are contradictory (Herin et al., 2014, 940-941; Haukka et al., 2012, 487-488) and therefore no certain conclusions cannot be made yet. In this thesis was found out also that participants with more pain sites took prescription medication more often in general and had more often pain lasting more than 12months when compared to participants with less pain sites.

In total 35% (147/302) of the participants with multi-site pain had a clinically meaningful improvement in neck and/or back pain at the follow-up at 6-months. The conclusion of the analysis is that multi-site pain did not affect the recovery on the treatment of neck and/or back pain neither at the follow-ups at week 7 or at 6 months, meaning that multi-site pain does not affect the prognosis on the treatment of neck and/or back pain.

Results from the earlier studies are contradictory and limited. Multi-site pain has been researched mostly in observational studies without intervention. In the event that treatment or intervention was provided, it was not reported clearly or systematically enough. There are no previous studies to the knowledge of the authors of this thesis that would have investigated the prognostic effect of non-specific musculoskeletal pain in other body sites on the treatment of non-specific neck and/or back pain in a similar way and extent as in this thesis. The possible impact on the treatment of neck and back pain therefore stays unclear.

In a study of 323 patients, the aim was to find out predictive factors for 1-year outcome of low back pain and neck pain in patients treated in primary care either with chiropractic treatment or physiotherapy. In the study was found out that the number of pain sites (total maximum of 3: neck, thoracic and lumbar) had a significant association with a poor outcome at the 1-year follow-up. The outcome was measured with the Oswestry low back pain disability questionnaire. (Skargren and Öberg, 1998, 203.) In contrary, a study by Enthoven et al. of 148 low back pain patients treated in primary care, the conclusion was that there was no prognostic value whether the patients had more than one pain localization. The aim was to identify predictive factors for disability after 1 and 5 years and other pain sites were defined as pain in the neck or thorax (maximum total of 3 pain sites). (Enthoven et al., 2006, 139-141.) However, in these both studies the small maximum number of other pain sites limits the comparability to this thesis.

Vasseljen et al. studied the natural course of acute neck and/or low back pain in the general population and the possible prognostic factors, of which one was the number of other pain sites (maximum of 12 sites). Those who reported four or more pain sites at baseline had only little change or no change

in pain at 12 months. Compared to the patients with more pain sites, those who had only one pain area had a faster decline in pain. However, the results of the study by Vasseljen et al. are not exactly comparable to this thesis since the treatment was optional and self-acquired. The patients were allowed to use medication and different treatment modalities (physician, psychologist, physical therapist, or chiropractor) and complementary treatments (homeopath, acupuncturist, osteopath, naprapath or other complementary therapists). Only one of five sought for treatment at some point during the follow-ups and they had only a little benefit from it. (Vasseljen et al., 2013, 1238-1240.) One systematic review that included only primary care-based cohort studies concluded that multi-site pain or widespread pain is associated with poor outcome across more than one anatomical site (Mallen et al., 2007, 656,658).

Many studies indicate that neck and low back pain are common and bothersome health conditions that are often accompanied with other musculoskeletal pain sites. What is known is that multi-site pain is very common and worse the prognosis of neck and low back pain, leading to work disability and functional disability (Coggon et al., 2013, 1773; Rathleff et al., 2013, 4; Kamaleri et al., 2009b, 428; Miranda et al., 2010, 451). What stays unclear is whether it has prognostic effect when treating neck and back pain. This under-researched population of patients with neck or back pain combined with multi-site pain is problematic. In comparison to patients with low back pain as their only ailment, they have more impaired general health, health related quality of life, and are more disabled (Ijzelenberg and Burdorf, 2004, 809). Somehow, manual therapists such as naprapaths or physiotherapists should be able to help these patients. Until the true prognostic effect and function of multi-site pain on the treatment of neck and back pain is known the treatment will not be based on any evidence. Multi-site pain as a comorbidity might be a manifestation of central sensitization and that is treated totally differently in contrast to neck or low back pain as a single site ailment. Causal connections, mechanisms and true effects of multi-site pain that is not labeled as chronic widespread pain or fibromyalgia are still unclear. It may not be possible or beneficial to select one pain site which is being the primary ailment and consider the other pain sites as comorbidities, but it is also one possible way of examining and unraveling the problem.

The possible prognostic value of multi-site pain on the treatment of neck and back pain has not been studied sufficiently extensively and systematically. The results are contradictory, and more randomized observational cohort studies are needed. No clear or certain conclusions can be drawn yet.

6.2 Methodological considerations

A potential systematic error is selection bias in a study, related to the procedures used to select subjects into this study population and from loss to follow-up. It occurs when the association between exposure and outcome differ for study participants and nonparticipants. (Rothman, 2012, 126.) A high participation rate with a low number of drop-outs in this study is a factor that increases the internal validity by lowering the possibility of a selection bias. The high participation rate in addition to the prospective study design ensures that the selection bias is unlikely to be a problem in this study. An exposure free group was not possible with our population because a group with no pain had not enough statistical power.

Misclassification in a study may appear because the information that is collected from study subjects may be incorrect. This might occur when an unexposed individual is categorized as exposed or an individual with disease is categorized as non-diseased and vice versa. (Rothman, 2012, 133.) A secondary analysis is always slightly more complicated since the data has been collected for another purpose in the first place. For instance, participants were focused on reporting neck and back pain since the primary study concentrated on those pain sites, not on the other musculoskeletal pain sites. This may lead to misclassification of exposure, since the complaints have been self-reported. A non-differential misclassification could possibly lead to a dilution of the associations towards RR=1. There was no data concerning the amount of pain sites at the follow-ups of weeks 7 and 24. Consequently it must be noted that the amount of pain sites could have changed during the follow-ups.

The definition of confounding is a confusion of effects, meaning that the effect of the exposure is mixed with the effect of another variable and therefore leading to a bias (Rothman, 2012, 137). Potential confounding factors might be a possible threat to the validity in observational cohort studies. Several potential

confounders were tested and only the duration of current episode was found to confound, thus the testing can be seen as strength in this study. There might be some unmeasured and residual confounding that were not tested which might influence the results. The effect of confounding could possibly lead to over- or underestimation of the results.

7 IN CONCLUSION

Participants with non-specific neck and/or back pain have often in addition non-specific musculoskeletal pain in other body sites. When treating neck and/or back pain, other non-specific musculoskeletal pain sites are not found to have a prognostic effect on the recovery. However, there are not sufficiently studies to support this statement. Non-specific musculoskeletal pain in other body sites is a modifiable factor; therefore, further study is needed to understand its effect on recovery.

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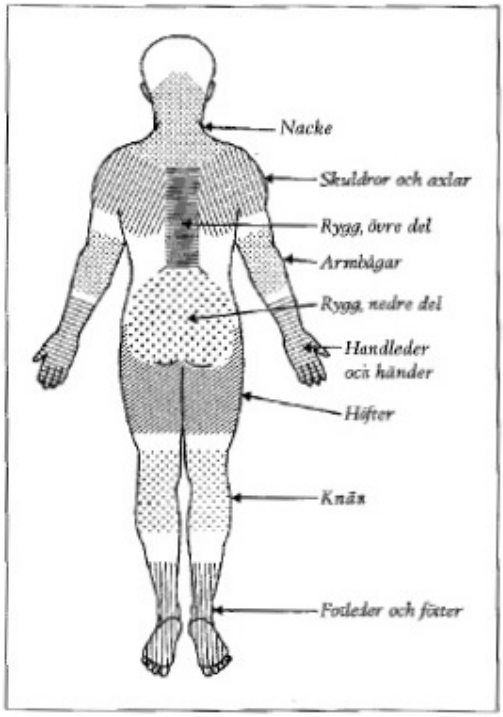
APPENDICES

Appendix 1. Section C1 questions in original language

C. ANDRA FRÅGOR OM DIN HÄLSA

Bilden visar det ungefärliga läget av de kroppsregioner som finns med i frågorna nedan. Begränsningarna av de olika kroppsregionerna är inte skarpa eller väldefinierade. Vissa kroppsregioner övergår i varandra. Du måste själv avgöra i vilken kroppsregion dina eventuella besvär sitter.



1. Har du haft besvär (smärta, värk, obehag) någon gång under de senaste 6 månaderna i:

a. Nacke?
☐ Nej ☐ Ja

b. Skuldror/axlar?
☐ Nej
☐ Ja i höger skuldra/axel
☐ Ja i vänster skuldra/axel
☐ Ja i båda skuldrorna/axlarna

c. Armbågar?
☐ Nej
☐ Ja i höger armbåge
☐ Ja i vänster armbåge
☐ Ja i båda armbågarna

d. Handleder/händer?
☐ Nej
☐ Ja i höger handled/hand
☐ Ja i vänster handled/hand
☐ Ja i båda handlederna/händerna

e. Ryggens övre del (bröstryggen)?
☐ Nej ☐ Ja

Appendix 2. Section C1 questions in original language (cont'd)

f. Ryggens nedre del (ländrygg/korsrygg)?
☐ Nej ☐ Ja

g. Höfter?
☐ Nej
☐ Ja i höger höft
☐ Ja i vänster höft
☐ Ja i båda höfterna

h. Knän?
☐ Nej
☐ Ja i höger knä
☐ Ja i vänster knä
☐ Ja i båda knäna

i. Fotleder/fötter?
☐ Nej
☐ Ja i höger fotled/fot
☐ Ja i vänster fotled/fot
☐ Ja i båda fotlederna/fötterna